Medical Staff Conference

Liver Transplantation—The First 25 Years

These discussions are selected from the weekly staff conferences in the Department of Medicine, University of California, San Francisco. Taken from transcriptions, they are prepared by Drs Homer A. Boushey, Professor of Medicine, and David G. Warnock, Associate Professor of Medicine, under the direction of Dr Lloyd H. Smith, Jr, Professor of Medicine and Associate Dean in the School of Medicine. Requests for reprints should be sent to the Department of Medicine, University of California, San Francisco, School of Medicine, San Francisco, CA 94143.

RICHARD K. ROOT, MD[*]: *Liver transplantation has recently moved from the realm of experimental therapy to that of effective therapy for certain forms of hepatic failure. This Medical Staff Conference, which brings us up to date with advances in this area, has been organized by Nancy L. Ascher, MD, Director of the Liver Transplant Program at UCSF, and her colleagues, John P. Roberts, MD, and John R. Lake, MD.*

NANCY L. ASCHER, MD, PhD[†]: This year marks the 25th anniversary of clinical liver transplantation; Thomas Starzl, MD, performed the first human liver transplant in 1963.[1] Although this sparked worldwide interest in the field, long-term survival was not attained until 1967.[2] Early one-year survival rates were poor, about 30%, until 1980 when cyclosporine was introduced as the principal immunosuppressive agent.[3] Using cyclosporine—as well as technical advances and improved patient management—ushered in survival rates of 65% from 1980 to 1984[3]; currently many centers report one-year survival rates of 80% or better.[4-6] After a 1983 National Institutes of Health consensus conference concluded that liver transplantation had become a therapeutic modality,[7] many states and private insurers began to pay for this procedure. Activity in the field has also increased from 26 transplants done in 1981 to more than 950 in the United States in 1987.

This review is intended to update readers on advances in this field, and we will attempt to provide insights into the striking increase in survival following liver transplantation. Readers must understand, however, that there have been few randomized trials concerning any aspect of clinical liver transplantation. Comparisons of patient selection, different surgical techniques, or immunosuppressive regimens depend on historical controls, comparisons between different centers using different techniques, animal studies, and local prejudice. Therefore, the validity is questionable.

Patient Selection

Careful selection of potential recipients and improved preoperative management have contributed to the improved transplant results. The selection process should be designed to answer three important questions: First, does the patient have a liver disease that is soon to progress to death or that

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significantly impairs the patient's quality of life and for which no alternative therapy exists? Second, are there medical contraindications present that would likely preclude a successful liver transplant? Finally, does the patient have the psychosocial characteristics necessary to comply with a postoperative immunosuppression protocol?

Appropriate indications for liver transplantation can be divided into general indications applicable to most forms of chronic liver disease and specific indications appropriate to one or only a few diseases (diseases for which liver transplantation has been done are listed in Table 1).[8-10] Indications for liver transplant that are applicable to most chronic liver diseases include ascites refractory to medical management, encephalopathy that significantly impairs life-style, variceal hemorrhage that is refractory to sclerotherapy, and the hepatorenal syndrome. Indications that apply to specific liver diseases include refractory pruritus (chronic cholestatic disorders such as primary biliary cirrhosis or extrahepatic biliary atresia), severe metabolic bone diseases with fracture (primary biliary cirrhosis),[11] recurrent cholangitis (primary sclerosing cholangitis or extrahepatic biliary atresia), neurotoxicity (Wilson's disease), and correction of metabolic diseases related to impaired synthesis of a liver-specific protein (familial hypercholesterolemia, tyrosinemia, α_1-antitrypsin deficiency, hereditary hyperoxaluria, the Crigler-Najjar syndrome type II).

Although these indications for liver transplantation are generally accepted, the decision regarding the exact timing of the operation is made difficult by the varying natural history of the liver disease.[8] Ideally, transplantation should be done at a time when a patient's general medical condition would minimize operative mortality and morbidity,[12,13] but where the liver disease severely jeopardizes one-year survival. Natural history data guide this decision. For example, patients with primary biliary cirrhosis may remain relatively free of complications until serum bilirubin levels exceed 10 mg per dl[14,15]; at that point, complications can be anticipated and a liver transplant should be considered. Similarly, in patients with fulminant liver disease, a prothrombin time of longer than 20 seconds or stage III encephalopathy (or both) indicate limited survival without transplantation.[16,17] Unfortunately, the natural histories of diseases such as chronic active hepatitis with cirrhosis or primary sclerosing cholangitis are much less predictable; consequently, decisions regarding the timing of transplantation are more difficult.

The contraindications for liver transplantation have evolved as the field has developed. Widely accepted contraindications include sepsis, extrahepatic malignancy, and advanced cardiopulmonary disease—such as an arterial oxygen pressure of less than 55 torr or pulmonary hypertension.[9,10] Many transplant centers regard a positive test for the human immunodeficiency virus (HIV) as a contraindication based on data showing that in HIV-positive patients who have undergone transplantation (before the availability of HIV testing), the acquired immunodeficiency syndrome often develops shortly after immunosuppressive therapy is instituted.[18]

Relative contraindications to liver transplantation include the presence of the hepatitis B surface antigen (HBsAg), hepatobiliary malignancy, portal vein thrombosis or other anatomic anomalies, a previous portacaval shunt operation, advanced age, renal failure, and active infection, although some centers pursue transplantation in these groups. Past experience indicates that the vast majority of HBsAg-positive patients retain or redevelop evidence of active viral replication after liver transplantation. Whether active or passive immunization protocols will affect this remains to be proved.[19,20] In addition, the incidence and natural history of recurrent hepatitis B virus disease in the graft are not yet defined. Primary hepatobiliary malignancy—that is, hepatocellular carcinoma and cholangiocarcinoma—is becoming a less frequent indication for liver transplantation due to the high incidence of tumor recurrence and poor long-term survival (20% survival at three years).[8,21] The fibrolamellar variant of hepatocellular carcinoma[22] and incidental tumors in children are exceptions. Experience with patients with portal vein thrombosis or a previous portacaval anastomosis

TABLE 1.—*Diseases for Which Liver Transplantation Has Been Done*

Adults	Children
Cirrhosis	Cirrhosis
Primary biliary cirrhosis	Biliary atresia
Chronic active hepatitis	Chronic active hepatitis
Cryptogenic cirrhosis	Cryptogenic cirrhosis
Secondary biliary cirrhosis	Caroli's disease
Primary sclerosing cholangitis	Congenital Hepatic Fibrosis
Alcoholic cirrhosis	Metabolic Disorder
Fulminant Liver Disease	α_1-Antitrypsin deficiency
Viral	Wilson's disease .
Drug-induced	Tyrosinemia
Toxin—such as *Amanita* mushroom sp	Glycogen storage disease
	Byler's disease
Metabolic Liver Disease	Sea-blue histiocytosis syndrome
Wilson's disease	Galactosemia
Hemochromatosis	Protoporphyria
Protoporphyria	Familial hypercholesterolemia
Hereditary oxalosis	Hepatobiliary Malignancy
Hepatic Vein Occlusion	Hepatoblastoma
Veno-occlusive Disease	Hepatocellular carcinoma
Hepatocellular carcinoma	
Cholangiocarcinoma	
Angiosarcoma	

indicates that these patients can successfully undergo a transplant operation, although often at the risk of increased perioperative blood loss. These cases require appropriate angiographic definition of the anatomy and careful preoperative planning. Elderly patients must be carefully examined for disease in other organ systems.[23] Patients with concomitant renal failure may require simultaneous renal transplantation.

Assessing a patient's compliance is difficult and varies with the experience and philosophy of the transplant program. Factors associated with poor compliance with immunosuppression regimens include active alcohol or other drug abuse, active psychiatric illness, or a history of poor compliance with medical treatments. For patients in whom compliance is an issue, a thorough psychological evaluation by trained professionals is mandatory.

Because decisions regarding the indications, timing, and appropriateness of liver transplantation are complex, most programs use a selection committee to assist in patient-selection decisions.[24] Selection committees typically comprise representatives from the departments of surgery, medicine, pediatrics, anesthesiology, intensive care, social work, pathology, psychiatry, nursing, and hospital administration. At the UCSF Medical Center, patient-selection committee meetings are monitored by a member of the lay public, and records of the proceedings of the meetings are maintained as a matter of public record.

Donor Selection

Currently there is a shortage of donors, particularly in the pediatric age group. At present, 30% of children who are acceptable candidates for transplantation die while waiting for a suitable donor liver.[25] With this shortage, it is important that all physicians be aware of the need for donation and approach the families of potential donors with the consideration of organ donation. In doing so, they may expect that the families will consent, as it has been estimated that more than 80% of families may choose to donate the organs of a relative if given this option.[26,27]

The main criteria for selecting a donor are ABO bloodtype compatibility (for stable recipients), the relative body size match, and the physiologic state of the donor. Although the organ from a person with blood type O (universal donor) can be used in any blood-type recipient, this practice should be avoided except for recipients who are deteriorating rapidly. This is to allow type O recipients the same chance to receive a liver as the frequency of the blood type in the general population because type O recipients can receive livers only from blood type O donors. Furthermore, there is a suggestion that the use of nonidentical but compatible blood group transplants may be associated with decreased survival.[28] In cases of dire need, ABO-incompatible donors may be used (primarily in type O recipients). Although this is associated with decreased survival, it is not clear whether the poorer survival results from selecting patients who are more gravely ill or from crossing the ABO barrier—resulting in increased rejection or requiring increased immunosuppression. At the University of Minnesota (Minneapolis) Medical Center, ten liver transplants from blood group A donors to group O recipients were done with a 70% one-year actuarial survival. All these transplants were carried out in patients with an urgent need for transplantation (N. L. Ascher, MD; J. P. Roberts, MD; and J. R. Lake, MD, unpublished data, July 1988). Splenectomy, antilymphocyte globulin, and ex-

change transfusions for rising anti-A titers in the first week following transplant were used prophylactically.

Donor-recipient size match is also important. Using a liver that is too large can lead to respiratory compromise and pressure necrosis of the graft. Using a donor liver that is too small may result in a mismatch of vessel size with a resultant relative stenosis. A recent advance in obtaining organs for pediatric patients is the partial resection of larger livers to fit into smaller recipients.[29]

One of the most dreaded outcomes of liver transplantation is primary nonfunction where the donor organ fails from the outset to produce coagulation factors or bile. Primary nonfunction is commonly fatal without immediate retransplantation. To avoid this catastrophe, an accurate assessment of the potential function of the donor liver is important. Tests that offer sufficient predictive power to allow discriminating between donor organs are currently lacking,[30] although work is progressing in this area.[31] A sensitive and specific method of predicting graft function may increase the pool of available donors, as many donor organs considered clinically unsuitable may actually provide good function after a transplant.

Current absolute contraindications to donation are a positive antibody to HIV, the presence of HBsAg, systemic malignancy, or sepsis.

Preserving the Donor Organ

Until recently, donor livers were preserved in a high osmolar, potassium-rich solution initially used for renal preservation. The mechanism of action of these solutions appears related to the impermeant solutes that maintain a relatively normal state of hydration of cells during preservation.[32] A new solution with a different set of impermeant substances—hetastarch, melitose (raffinose), and lactobionate—will likely extend the maximal preservation time from 10 hours to at least 20 hours.[33] Longer preservation times will create the possibility of intracontinental sharing, superior recipient preparation, and an unhurried approach to the transplant procedure. Extended preservation may allow local teams to procure a liver and ship it to a transplant center via scheduled flights. This would end the expensive use of chartered aircraft to transport donor livers.

Organ Sharing

In October 1987, a nationwide organ sharing system was instituted.[34] The system is structured so that possibly available organs are first offered to local programs. If no local recipient is available, then the organ is offered to centers within a defined geographic region. If no regional recipient is available, the organs are then offered nationally. The selection of recipients is based on criteria that allow for the level of care the recipients are requiring. Patients in an intensive care setting are assigned the highest priority. Patients who are still able to work are assigned the lowest priority.

Operative Technique

Orthotopic liver transplantation remains a surgical tour de force. Every aspect of the operation is fraught with potential complications. Much of the improved survival following liver transplantation can be related to improvements in the surgical and anesthetic techniques. The operation consists of three phases: mobilization of the recipient liver, the anhe-patic phase during which the vessels are clamped while the recipient liver is removed and the donor liver sewn in, and the period following revascularization of the donor liver.

The operative challenge of liver transplantation can be traced to two specific complications of chronic liver disease. First, there is impaired hemostasis from diminished hepatic synthesis of coagulation factors and thrombocytopenia resulting from portal hypertension with hypersplenism. Second, portal hypertension also produces increased venous collaterals, which are often most severe when there are adhesions and scars from previous operations. The combination of large nests of vessels to divide and the lack of coagulation factors and platelets to provide hemostasis leads to the possibility of extensive blood loss. The technical problems of recipient hepatectomy are compounded in patients with previous right upper quadrant operations. If patients are possible transplant candidates, a right upper quadrant procedure should be deferred, particularly central portosystemic shunts.

The anesthetic management is directed toward maintaining an adequate intravascular volume and a functioning hemostatic system. This requires supplementing clotting factors with fresh frozen plasma and cryoprecipitate and correcting thrombocytopenia. Anesthesiologists also must be able to administer large volumes of blood and blood products rapidly. The development of the rapid transfusion device has allowed for the delivery of warmed blood at a rate greater than 2 liters per minute.[35] A third anesthetic problem is maintaining a normal electrolyte balance. Hypocalcemia from receiving large volumes of citrated blood, acidosis, and hyperkalemia from reperfusion of the donor organ and from the banked blood are common intraoperative events.

Venovenous Bypass

When liver transplantation was first attempted in animals, it was found that normal dogs did not tolerate prolonged clamping of the portal vein and inferior vena cava. Hemodynamic instability led to the development of a method of shunting the blood from the portal vein and inferior vena cava to the superior vena cava (venovenous bypass).[36] This provided the hemodynamic stability necessary to complete the operation. Later work showed that bypass was not necessary in dogs that had preexisting portal hypertension. Many humans also tolerated vessel clamping without the use of the bypass. In liver transplantation, clamping of the portal vein and infrahepatic vena cava has three undesirable effects: a loss of preload from a decreased venous return, an increase in the vena caval pressure that theoretically can impede renal venous return and compromise renal function, and bowel edema from obstructing the portal system. Because of these problems, the Pittsburgh group reinstated the use of the bypass, first in heparinized patients (which led to excessive bleeding), then in those who had not received heparin.[37] The incidence of renal dysfunction and blood loss was diminished in their patients with the use of the bypass as compared with historical controls.

Other groups have reported successful liver transplantation without using a bypass and without an increase in renal dysfunction or blood loss.[4,38] It is possible to overcome the loss of preload and maintain good urinary output during the anhepatic phase without bypass by using the rapid transfusion device. Advocates of the bypass describe the major ben-

efit as allowing for an extended anhepatic phase when training surgeons or in difficult technical situations.[39]

The use of the bypass is not without risk. Pulmonary embolism, nerve injury, lymphoceles, and wound infections have all been reported as complications. The specific benefits of the bypass are unclear and would have to be determined in a randomized trial.

Biliary Reconstruction

The biliary drainage procedure is responsible for most of the complications following liver transplantation. In early reports of liver transplantation, an incidence of 34% to 53% and a mortality of 25% to 30% occurred from biliary tract complications.[40,41] The incidence of biliary complications has decreased to 12% to 13%.[42,43] Improvements have come from standardizing the reconstruction of the biliary tract to either a choledochocholedochostomy—donor bile duct to recipient bile duct—in recipients with normal bile ducts or a Roux-en-Y choledochojejunostomy in those patients with abnormal bile ducts, such as patients with extrahepatic biliary atresia or sclerosing cholangitis.

Biliary complications require immediate intervention to divert the bile, usually done by transhepatic biliary drainage and drainage of any associated bile collections. A disruption of the anastomosis requires revision while late strictures may be managed by balloon dilatation and stenting. Two caveats have been suggested in cases of biliary complications. The first is that ultrasonography may be unreliable in diagnosing biliary tract dilatation in a liver transplant recipient,[44] and, second, the presence of biliary tract problems should raise the possibility of a hepatic artery thrombosis.[45]

Hepatic artery thrombosis. Because liver transplantation interrupts the arterial collaterals to the liver, subsequent thrombosis of the hepatic artery results in a total loss of arterial blood flow to the hepatic parenchyma and the biliary tree, leading to hepatic necrosis and biliary complications. The resulting biliary tract lesion resembles sclerosing cholangitis with bile duct strictures and dilatation. The incidence of hepatic thrombosis is about 3% to 10%, with a higher rate in pediatric patients and in patients with complex vascular reconstructions.[46] Hepatic artery thrombosis occurring immediately after transplant is particularly hazardous as new collaterals have not developed; the mortality in this setting is 50%. Current emphasis has been on early detection by the use of electromagnetic flow probes to recognize decreased flow in the hepatic artery,[47] the use of Doppler ultrasound to test for arterial patency in the postoperative period, and the use of aspirin to prevent thrombosis.

Thrombosis in the immediate postoperative period usually requires retransplantation, although it is possible that early recognition, a thrombectomy, and an anastomotic revision may preserve the liver and biliary tree.[48] Late thrombosis may lead to abscess formation and biliary strictures or follow a more benign course, possibly due to the development of collaterals to the liver.

Portal vein thrombosis. Thrombosis of the portal vein occurs in 1.8% of transplants and carries a better prognosis than hepatic artery thrombosis. Liver function may be maintained, but portal hypertension and variceal hemorrhage frequently develop. The Pittsburgh group currently recommends conventional treatment for varices in those patients who have normal liver function following portal vein thrombosis.[49]

Nonsurgical Complications in the Immediate Postoperative Period

Renal dysfunction is common in the posttransplant period. Some series report the need for dialysis in 25% of patients after a transplant.[50] Immediate renal dysfunction in liver transplant recipients is often related to the use of cyclosporine. Acute cyclosporine toxicity is mediated by a reduction of renal blood flow and the glomerular filtration rate.[51] This action is manifested clinically by oliguria accompanied by a low fractional excretion of sodium. This can result in significant salt and water retention despite the presence of hypervolemia and a salt and water excess due to intraoperative crystalloid and colloid use. Our approach to this problem is to administer intravenous cyclosporine continuously beginning at a dose of 0.25 mg per kg body weight per 24 hours, with a gradual increase in the dose to a maximum of 3 mg per kg per 24 hours. To overcome the renal salt retention, intravenous furosemide and dopamine hydrochloride are administered to maintain a good urine output, euvolemia, and a return to near the preoperative weight within 72 hours. If the urinary output remains low, the cyclosporine therapy is discontinued for four hours and reinstituted at a lower dose when the urinary output returns to normal. This approach has led to an incidence of posttransplant dialysis of less than 5% at the University of Minnesota and UCSF.[4] The use of lower doses of cyclosporine is possible because of the concomitant use of azathioprine in the postoperative period.

Infection

Infectious complications are common with the use of immunosuppression. It is estimated that, on average, at least one episode of bacterial infection will develop in a patient with a liver transplant, and there is a 40% to 50% chance that fungal or viral infections will develop.[52]

The sources of bacterial infections are generally the biliary tree, intra-abdominal abscess, pneumonia, and central venous catheters.[4] These infections are often associated with complications of the liver transplant; the result of decreasing technical complications should be a decrease in the number of bacterial infections.

Pneumocystis carinii pneumonia is an important problem in transplant patients. These infections can be eliminated in immunocompromised patients through the prophylactic use of trimethoprim and sulfamethoxazole.[53] Intermittent therapy—three times a week—has recently been shown to be as effective as daily therapy in decreasing fungal infections.[53] With prophylaxis, *P carinii* morbidity and mortality should be eliminated in transplant patients.[54]

Viral Infections

Viruses of the herpes family are the most common viral pathogens following a transplant. Herpes simplex and varicella-zoster virus infections generally present with mucocutaneous manifestations, and therapy with acyclovir appears to be effective. More serious infections occur with the cytomegalovirus (CMV). The onset of CMV infection generally occurs within the first two months. In one report, 9 of 12 patients in whom CMV infection developed were symptomatic.[55] The infections that appear to be particularly serious are those in patients with negative CMV serologic tests before transplant (primary infections). These patients appear to acquire the infection from either a seropositive liver donor or blood donors. The ability to protect seronegative recipi-

ents from primary infection appears to be possible through the use of seronegative liver and blood donors, but the availability of large amounts of CMV-negative blood products is limited. Using the new antiviral agent ganciclovir has been reported to be effective in serious CMV infections following liver transplantation.[56]

Mechanisms of Liver Transplant Rejection

The incidence of liver transplant rejection ranges from 20% to 80% depending on the criteria used to make the diagnosis. Some groups require only histologic evidence of rejection while other groups require histologic changes in association with clinical manifestations or laboratory abnormalities or both. The classic histologic features of liver transplant rejection are primarily seen in the portal triads.[57,58] Portal-based cellular infiltrate, bile duct epithelial damage, and central vein and portal vein endotheliitis are the most common features of rejection. The sites and distribution of the human leukocyte antigens within the liver correlate with the histologic picture of rejection and are felt to be of importance in the pathogenesis of rejection. Bile duct epithelium and central vein endothelium are rich in class I and class II antigens, and increased antigenic expression can be noted during acute rejection.[59] Hepatocytes have modest amounts of class I expression and virtually no class II expression even during acute rejection. This may explain why hepatocyte injury is seen only late in the rejection process.

An example of the specificity of the rejection process for the portal tracts and particularly for the bile ducts is seen in the histologic features of the "vanishing bile duct" syndrome occasionally seen in cases of liver transplant rejection. In this variant of chronic rejection, an intense inflammatory reaction destroys the bile ducts, and after the bile ducts "vanish" the inflammatory cells also disappear, as if the bile duct epithelium were the only target of the inflammatory cells. The histologic finding following this rejection process is of hepatocytes that appear normal and portal tracts without inflammatory cells but also without bile ducts.[60]

A further refinement over identifying lymphocytes within the portal tract during rejection is the use of lymphocytic antigenic markers to identify specific lymphocyte subsets. Perkins and co-workers found that the patterns of T-helper cells alone or a combination of T-helper and T-cytotoxic/suppressor cells within the portal tracts predicted for and antedated clinical manifestations of rejection.[61] Thus, the current evidence supports a major cellular component in the rejection of liver allografts. The cellular rejection appears to be of the classic type, initiated by T-helper cells, which are stimulated by class II antigens in the bile duct epithelium and central vein endothelium, and effected through T-cytotoxic cells whose activity is directed against class I antigens present on bile duct epithelium, central vein endothelium, and less intensely on hepatocytes.

The role of antibodies in acute or chronic liver rejection is uncertain. The presence in a recipient of a preformed antibody against donor antigens does not adversely affect the liver allograft outcome.[62] The depletion of high antibody titer or inducer cells that amplify the antibody response can accompany the blood loss that frequently occurs during transplantation and may dampen the antibody's effect in graft injury.

A diagnosis of rejection based solely on histologic findings remains controversial. Until a randomized trial is carried out subjecting patients with histologic changes alone to either treatment or observation, the significance of histologic changes will remain unknown. Laboratory abnormalities, however, have been nonspecific in a number of studies; they do not differentiate rejection from other causes of hepatic dysfunction.[63] Clinical signs and symptoms of liver transplant rejection are equally nonspecific. Fever, a decreased bile output, a change in bile consistency, graft tenderness and swelling, increased ascites, and a decreased level of consciousness have all been reported to accompany rejection but are not specific. The group at the University of Minnesota reported on 58 consecutive patients who underwent weekly percutaneous biopsy after transplants to diagnose rejection. Treatment was instituted based on the histologic diagnosis of rejection. The incidence of biopsy-proved rejection was 77% in adult patients and 73% in pediatric patients. Moreover, with this aggressive approach, the incidence of patients requiring retransplantation for chronic rejection was less than 5%.[4] This compares favorably with a 20% to 25% retransplantation rate in other programs.[64] Moreover, despite the frequent need for the treatment of rejection, the death rate from infection following transplantation was only 11%.

Preventing Rejection

The agents used to prevent liver transplant rejection are the same ones used to maintain other whole-organ grafts. The current mainstay of immunosuppressive programs is cyclosporine, and most regimens involve combining two or more drugs to maximize immunosuppressive synergy and minimize drug toxicity. Cyclosporine, a cyclic endecapeptide first described by Borel and colleagues in 1977,[65] has profound inhibitory effects on interleukin-2 production and inhibits T-cell proliferation. This blocks amplification of the rejection reaction, dampening the full-blown rejection response. The side effects of cyclosporine use include nephrotoxicity, hypertension, hirsutism, hypertrichosis, gingival hyperplasia, malignancy, hand tremors, painful paresthesia of palms and soles, benign fibroadenomas, and hepatotoxicity. Many of these complications are dose related and can be resolved with dose modification.

Steroids continue as a major component of the antirejection regimen, acting at several levels of the immune response, including antigen processing and presentation, inhibition of lymphocyte proliferation, and decreased expression of class II antigens. The side effects of steroid use include sodium retention, hypertension, impaired wound healing, increased infections, and glucose intolerance. Azathioprine, an antimetabolite, inhibits cellular proliferation and is often used in conjunction with prednisone and cyclosporine. Its suppressive effects on the bone marrow can be titrated along with its dose.

Treating Rejection

The optimal therapy for liver transplant rejection has not been determined. According to the Boston Consortium Study, many first-time, mild rejection episodes can be successfully treated with increased doses of steroids. Continued rejection or subsequent rejections are best treated with antilymphocyte globulin or monoclonal OKT3 antibodies.[66] Administering these antilymphocyte preparations, though successful in treating rejection, is associated with an increased incidence of viral infections.[4]

Summary

Improved survival following liver transplantation in the 1980s has not been the result of any one advance. Earlier patient referral and better patient selection have led to recipients who are likely to be long-term survivors following a transplant while not eliminating those marginal patients who will benefit from it. Improvements in donor organ recovery have increased the pool of acceptable organs available and, therefore, have decreased waiting time, allowing transplantation before the irreversible deterioration of a recipient. Better operative techniques have led to fewer complications, and techniques of anesthetic management have decreased intraoperative death and postoperative morbidity. Immunosuppression and the treatment of rejection have improved, resulting in a decrease in retransplantation, making more organs available to other patients while not increasing the complications of immunosuppression.

These advances have occurred in an accelerated fashion since 1980. It would be expected that a plateau in improvements has not been reached yet, and the 1990s will herald not only improved survival but decreased costs, complications, and hospital stays.

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